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Preliminary Communication.

The following results are part of a research which has for its object the determination of the physiological action not only of pyridine but also of its congeners piperidine and propyl-piperidine or coniin; but since this research must necessarily be a somewhat long one we thought it wiser to publish our results with pyridine in the form of a preliminary communication.

The physiological action of pyridine is of peculiar importance because it may be regarded as the nucleus of many of the organic alkaloids. The pyridine used was kindly given to us by Mr Gordon Salamon and examined by Dr Hugo Müller. Dr Müller finds that with the exception of some picolin, and some higher homologues, it is a pure specimen.

General action on frogs. The drug even in relatively small doses ·01 gramme has a general narcotic action on frogs. If the dose is increased to ·02 to ·04 according to the size of the frog death takes place, voluntary movements ceasing in about 4 minutes and respiratory movements ceasing in from 10 to 15 minutes. The heart continues beating long after this (1—2 hours) although with irregular rhythm and diminished force. This is in accordance with the results of Distler[1] who found that the heart remained long unaffected by the poison. The fact that no spontaneous muscular movements nor convulsions were observed does not agree with the results of Harnack and Meyer[2]; this discrepancy may be possibly explained by differences in the specimen of pyridine used.

[1] Distler. "Ueber einige Wirkungen des Pyridins." Inaug. Dissert. Erlangen, 1877.

[2] Harnack and Meyer. *Arch. f. exp. Path. u. Pharm.* XII. 366.

General action on guinea-pigs. Pyridine is lethal to guinea-pigs in doses of ·087 gramme of pure pyridine per 100 grammes body weight when injected into the peritoneal cavity. Much larger doses are required when the drug is introduced into the stomach, e.g. ·4 gramme per 100 grammes body weight.

After administration of the drug, a more or less profound narcosis is produced, which comes on with a rapidity varying from 2 to 20 minutes according to method of administration. Peripheral sensation both in the skin and the mucous membranes is very much reduced but is never quite abolished, the conjunctual reflex is often the least affected.

Spontaneous muscular tremors were only very occasionally observed, but tremors were often elicited in response to powerful peripheral irritation. Death finally takes place from respiratory failure.

In the profounder stages of pyridine poisoning the whole animal feels cold, the coldness being especially marked in the extremities. This observation led us to endeavour to determine whether pyridine had any action in depressing the normal bodily temperature.

The temperature of rabbits was taken per rectum during pyridine poisoning and no appreciable change was noted. It was found with pyridine as with chloral that the fatal issue could be considerably postponed by keeping the animal warm.

In our experiments upon the special action of pyridine the order of the following paragraphs was observed.

Action on muscle. Pyridine seems to have practically no action on striped muscle. The curarized sartorii of frogs left in 100 c.c. of a ·2 % solution of pyridine in ·6 % saline solution[1] for from 1½ to 3 hours showed no diminution of irritability as compared with curarized sartorii immersed for the same length of time in ·6 % saline solution.

If curarized frogs were subsequently pyridined one leg being protected from the pyridine by ligature it was found that there was practically no difference in the direct irritabilities of the two gastrocnemii. The proof that the poison had reached the non-protected limb was furnished by the fact that the respective gastrocnemius smelt of pyridine.

Action on motor nerve endings. Pyridine has a paralysing action on motor nerve endings. This action is slight, so slight, that in cases of general poisoning an amount of the poison sufficient to cause paralysis does not reach the muscles. In other words it is only by the method of local application that one can demonstrate this effect.

Sensory nerve endings. Pyridine has a very marked paralysing

[1] The saline solution used was not free from lime.

action on sensory nerve endings and exerts this both when injected into the general circulation and when applied locally.

A 5% solution of pyridine applied for two minutes to the right leg of a decapitated frog weighing 17 grammes produced complete local anæsthesia which lasted for 20 minutes.

When pyridine is introduced into the general circulation in doses which are insufficient to cause paralysis of the sensory centres of the cord (see below), the order of the onset of the skin anæsthesia seems to be hind limbs, then fore limbs, and then trunk.

Sensory spinal centres. Pyridine paralyses the sensory centres of the cord in frogs, when injected into the circulation in doses of from ·09 to ·1 gramme per 100 grammes body weight. The skin becomes anæsthetic as described above, but in addition, stimulation of the central end of the sciatic by an induced tetanizing current remains inactive.

Motor centres and motor conductivity of the cord. If the spinal cord of decapitated and pyridined frog be exposed and stimulated directly by a weak induced tetanizing current, convulsive contractions will take place; these contractions will first make their appearance at the level of the stimulation, but these will be immediately followed by contraction of the lower limbs. Both of these sets of convulsive contractions will take place at a stage of the poisoning when neither irritation from the skin nor irritation from the central end of the divided sciatic, will cause any reflex action.

Thus if we consider the different parts of the reflex arc, sensory nerve endings, afferent nerve, sensory spinal cells, intermediate fibres, motor cells, efferent nerve, and lastly motor nerve endings, we see that pyridine, when introduced into the general system, paralyses the sensory nerve endings, the sensory spinal centres or possibly the intermediate fibres, leaving the other constituents of the arc intact at least in frogs.

In guinea-pigs it would seem, from the fact that occasionally more or less general tremor occurred in response to strong peripheral irritation, that, either the activity of the motor centres is somewhat increased or that some change has taken place in the conducting activity, the relative resistance, of the intermediate fibres.

Automatic respiratory centre. Pyridine in relatively small doses ·05—·1 gramme pro kilo body weight has a marked action on the automatic respiratory centre. The respirations become slower and shallower, they then become irregular and inspiration takes place in two phases with a slight pause between them. This causes a notch in the otherwise continuous ascent of the lever making the descent of the

diaphragm during inspiration. If a larger dose be given this respiratory irregularity soon ends in respiratory failure.

Vagus respiratory centre. The action of pyridine upon this centre does not seem to be quite constant. The action of the anæsthetic is difficult to eliminate; it seems however that pyridine has a tendency to diminish the activity of the inhibitory (expiratory) portion of the vagus centre when it is stimulated by weak induced tetanizing currents. If the stimulating currents are stronger this is not the case, a complete arrest of respiratory movements in expiration takes place, and the strength of current required to produce this is much less when the animal is under pyridine and ether than when under ether alone.

Circulation. Pyridine has a marked but transient effect upon the circulation. Almost immediately after the injection of from ·5 to 1 c.c. of the 10 % solution pro kilo body weight a marked fall of blood pressure takes place. The extent and rapidity of onset of this fall are dependent, not only upon the dose, but upon the point of injection, and upon the vascular tension at the time of the injection. This fall amounts to from 15 to 30 mms. of mercury. It occurs when the spinal cord is divided at the occipito-atlantoid joint, when the aorta is compressed, and also when the vagus endings in the heart are paralysed by the previous injection of atropine.

From the above it appears that this fall of blood pressure is due to a paralysing action exerted by the drug on the cardiac muscle, and this is supported by the results of experiments on the excised frog's heart. If to a ·6 % solution of NaCl in New River tap water containing 2 c.c. of a 1 % solution of KCl to every 100 c.c. pyridine be added in the proportion of ·1 %, the cardiac beats become slower and their volume becomes increased; if the strength of the pyridine be increased to ·3 %, the beats become much slower and are irregular in volume and rhythm; upon still further increasing the pyridine the beats become smaller and more irregular, and the heart is finally arrested in diastole. The drug has precisely the same effect when circulated through a previously atropined heart. After the heart's action has been arrested for three quarters of an hour, it can be restored practically to the normal, by circulating through it New River tap water saline and potassium chloride solution (Ringer's solution). Small doses (·1 %) have a distinct tonic action upon the excised frog's heart, slowing the beat and increasing its volume, and also increasing the absolute strength of the heart, *i.e.* the height to which it can pump a column of water. We must then conclude that the action of pyridine upon blood pressure is due to its action on the heart.

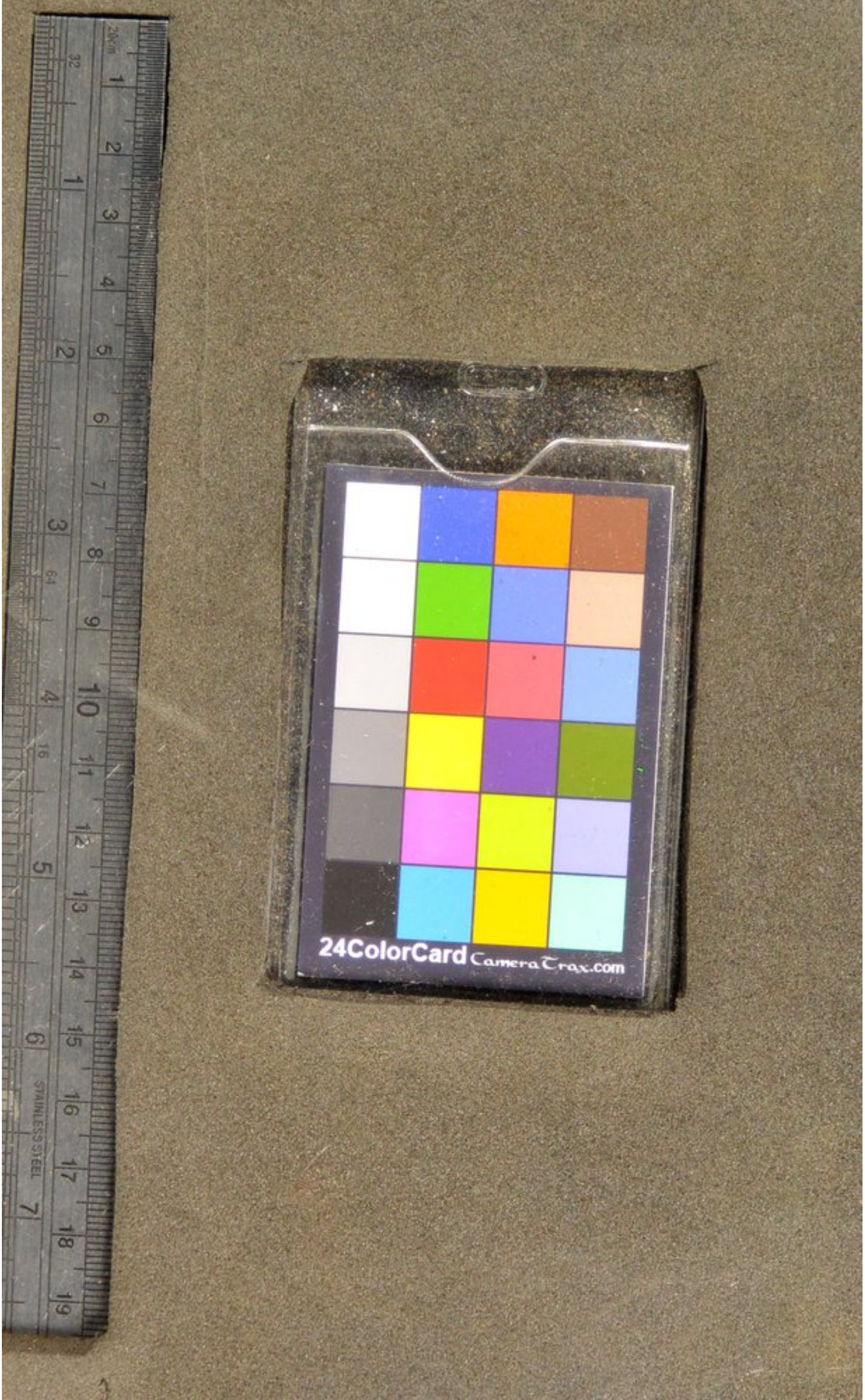
Action on the vaso-motor centre. Stimulation of the central end of the divided sciatic nerve during pyridine poisoning causes not a rise but a fall in blood pressure. Stimulation of the central end of other sensory nerves has the same effect, and this effect is quite constant. This action has long been known in the case of chloral.

As a result of the above we are able to formulate the following conclusions:

1. Pyridine is not, as compared with its derivatives, an active poison. This would hardly be expected *a priori* as it is an exceedingly stable body.

2. Its action is almost confined to the sensory part of the nervous system.

3. It has in small doses a stimulating, and in large a direct paralysing, action on the cardiac muscle.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